Justification for Retraction of HED Memo "Literature Review on Neurodevelopmental Effects and FQPA Safety Factor Determination for the Organophosphates"

In September 2015, the Health Effects Division (HED) of the United States Environmental Protection Agency (EPA) Office of Pesticide Programs issued a literature review of organophosphate (OP) pesticides (herein referred to as the "Literature Review") that claimed that certain epidemiology data created uncertainty in the context of the Food Quality Protection Act (FQPA). Based on that conclusion, the 10X FQPA safety factor was reinstated for all OP pesticides. In its previous evaluations of the same epidemiology data, EPA declined to use these data in any substantive way in regulatory decision making, which suggests the conclusions in the 2015 Literature Review were driven by ad hoc policy, rather than by science or well defined policy.

In 2017, the EPA Administrator appropriately halted the improper use of selected epidemiological study outcomes to revoke tolerances for chlorpyrifos, citing "serious scientific concerns." Unfortunately, the flawed 2015 Literature Review continues to cloud the public record and creates a significant misperception of potential risk from the use of OP pesticides. The public, the courts, and now other regulatory agencies are drawing improper conclusions about the data because the record has not been corrected. Accordingly, the Literature Review should be retracted and withdrawn from the public record.

The basis for this retraction and major concerns include the following:

- It is scientifically indefensible to revoke tolerances and cancel registrations for chlorpyrifos based on the flawed epidemiology studies reporting neurodevelopmental effects. Moreover, it is completely inappropriate to bridge these studies to all OPs for application of a 10X FQPA safety factor in the absence of confirmed exposures and a plausible mode of action.

- The legislative definition of safety has been arbitrarily reinterpreted. The legal standard for a safety finding is "reasonable certainty of no harm," based on an available and reliable database. The legal standard is not the precautionary principle. The presence of unreliable literature does not diminish the ability to reach a determination of reasonable certainty of no harm based on other, scientifically sound evidence.

- HED justified blanket reinstatement of the 10X FQPA safety factor to all the OPs based primarily on its use of select results of three epidemiology studies out of an extensive number of such publications. Studies showing null associations or positive outcomes were inappropriately weighted, discounted, or not considered (i.e., recently reported studies).

- The heavily-weighted Columbia study appears to have omitted data, and the results cannot be validated because the study authors continue to refuse to release the raw data for independent review by EPA or other interested parties.

2200 PENNSYLVANIA AVENUE, N.W. ◆ SUITE 100W ◆ WASHINGTON, D.C. 20037 ◆ TEL 202.557.3800 ◆ FAX 202.557.3836

A new independent analysis of the Columbia study (by Toxicology Excellence for Risk Assessment) shows that up to 35% of the data, including four high dose data points, are missing from the published figures in the Columbia study. Also, the published data were adjusted in a manner not typically used in risk assessment. Simply replotting the data in a more conventional manner diminishes or eliminates the alleged associations between chlorpyrifos levels in the mother's cord blood and lower memory and IQ scores in their children.

- HED has acknowledged that there is no plausible biological explanation for the reported neurodevelopmental associations. In the absence of an experimentally demonstrable and accepted common mode of action/adverse outcome pathway, there is no basis for bridging any of the exposure outcomes alleged in the epidemiology studies from one OP to another.

- In 1996, Congress added in FQPA the need to identify a common mechanism of toxicity. The criteria for identifying a common mechanism of toxicity for risk assessment were clearly defined by the Agency in its 1999 *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*. However, these criteria were ignored in the Literature Review. In contrast to the rigorous process used previously to group the OPs for an assessment of cumulative risk from cholinesterase inhibition, HED has not in this case identified any specific common parameter of toxicity such as the toxophore, or bioactivation pathway, or either specific toxic action/site of toxic action that could lead to the alleged neurodevelopmental outcomes.

- Complex and disparate behavioral outcomes such as autism spectrum disorder, ADHD effects, social responsiveness issues, and IQ detriments have essentially all been treated as the same neurodevelopmental outcome or "endpoint" by EPA, when in fact the respective etiologies and risk factors for each of these outcomes are likely very different.

- Reported associations that are based on nonspecific dialkyl phosphate biomarkers (DAPS) are inappropriate for use in regulatory decision-making. There is no way to track the DAP biomarkers to any specific OP; moreover the presence of urinary DAPs may simply reflect exposure to preformed metabolites that can be present in foods at higher levels than parent molecules and can seriously confound interpretation of the urinary DAP data. Because the reported urinary DAP data are not reliable, the reported associations also are not reliable.

- HED acknowledged in the Literature Review that multiple socioeconomic risk factors that are unrelated to pesticide exposure, or exposures to various environmental toxicants, could confound the reported associations. However,

the implications of such potential confounding on the interpretation of results were given scant weight in that review.

- Potential confounding of the reported neurodevelopmental outcomes by environmental contaminants other than DAPs was recently evaluated by the Exponent group (2016, *An Analysis of Potential Confounders in* Organophosphate *Epidemiologic Studies)*. Its analysis shows that children with generally high urinary DAP levels may also have generally high levels of phytoestrogens and exposures to other contaminants, such as polycyclic aromatic hydrocarbons (PAH) and lead. Without explicit analyses to exclude these variables as confounders, the reported associations between DAP levels and neurodevelopmental outcomes are potentially erroneous and no definitive conclusion can be drawn. In fact, in separate publications by many of the same authors of the Columbia Rauh *et. al.* publications regarding the study of chlorpyrifos, the same authors with Frederica Perera as the lead author have published articles involving the same cohort but claiming an effect on neurobehavioral development and exposure to airborne PAHs (Perera, F. *et al.*, Environmental Health Perspectives, 2006; Vol 114(8):1287-1292 and Perera, F. *et al.*, Pediatrics, 2009; 124:105- 202). In a separate publication (JAMA Psychiatry. 2015;72(6):531-540), the authors again used the same cohort of children to suggest that prenatal exposure to PAH air pollutants contributed to cognition and behavioral problems by disrupting development of white brain matter.

- EPA's own Scientific Advisory Panel raised concern about "the failure to reliably account for a number of key confounding factors, most notably gestational age" in the Columbia study, "calling into question the reliability of conclusions reported in the Study's published articles."

- EPA should consider how other Federal Agencies handle the use of epidemiology data. The U.S. Food and Drug Administration (FDA) frequently considers epidemiology publications and has guidance for use of such information (*Toxicological Principles for the Safety Assessment of Food Ingredients, 2001*). FDA considers that "the results of correlational studies would be insufficient to demonstrate a relationship without other types of data to support them." The absence of a plausible mode of action for the alleged neurodevelopmental outcomes precludes the identification of supportive data.

- The Literature Review is presented as a systematic review of published epidemiology data. The FDA does similar reviews of epidemiology data, which they describe as meta-analysis. The FDA guidance states that "The Agency must carefully scrutinize each meta-analysis to assess the soundness of its design and the quality of the data from individual studies to determine the significance of the data. Such scrutiny requires review of the original

studies used for the meta-analysis." EPA should do a similar analysis. However, the researchers for the epidemiology data cited in the Literature Review have declined to release the raw data. A true meta-analysis of the published epidemiology data cannot be undertaken without the raw data. EPA should not rely on these epidemiology data until it can independently confirm the data and results.

- HED claims that the neurodevelopmental associations alleged in the epidemiology studies of OPs create uncertainty; however, this is not the case. Rather, the many limitations of these epidemiology studies render their results unreliable and, therefore, unusable for hazard and risk assessment. These limitations do not create uncertainty, particularly the type of uncertainty that the FQPA safety factor is meant to address; instead, they simply cast further doubt on any claim of causation.

- The reported epidemiology study outcomes cannot be verified by independent review of the raw data. Accordingly, the epidemiology data do not meet the legal standard of reliable and available data. In contrast and by EPA's own admission, the OP regulatory databases (*i.e.*, GLP required animal toxicology studies) are complete and robust. These databases include studies specifically designed to quantify any susceptibility differences between adults and children. EPA previously relied on the regulatory studies to reduce or remove the 10X FQPA safety factor. The weak epidemiology data do not negate the strength of the available and reliable regulatory data. The existing databases for the OPs continue to be sufficient to justify the removal or reduction of a 10X FQPA safety factor and for making scientifically and legally defensible safety findings.

- Using epidemiology studies with no confirmed exposure, consistency of effects, or plausible biological explanation as the new standard for retaining the 10X FQPA safety factor is not consistent with the requirements of the law or Congressional intent and would result in EPA never being able to remove or reduce the FQPA 10X.

In view of the above concerns, the Literature Review should be retracted.

Background

Since the Food Quality Protection Act (FQPA) was enacted in 1996, data derived from GLP-conducted animal studies have supported the decision on whether to retain, reduce, or remove the 10X FQPA safety factor. For most organophosphates (OPs), EPA reduced the FQPA safety factor from 10X to 1X based on complete databases and no indication of increased sensitivity, though a few had 3X FQPA factors for a missing study or evidence of some increased sensitivity. In December 2014, EPA reversed its position regarding the use of animal studies as the primary driver for use of the 10X FQPA, and

directed the use of specific epidemiology studies/papers to support a contention of "uncertainty" in its human health risk assessments. EPA has since ignored concerns raised by numerous EPA Scientific Advisory Panels (SAPs) and impacted stakeholders, and adopted a position in direct contrast with those that the Canadian Pest Management Regulatory Agency (PMRA) and the Australian Pesticides and Veterinary Medicines Authority (APVMA) have taken with respect to the same epidemiological studies. EPA contends that the collective epidemiological evidence supports concern and uncertainty over putative neurodevelopmental effects in humans and has therefore reapplied the 10X FQPA safety factor to all OPs. EPA's rationale is described in a Office of Pesticide Programs (OPP) Health Effects Division (HED) memo titled "Literature Review on Neurodevelopmental Effects and FQPA Safety Factor Determination for the Organophosphates," (herein referred to as the "Literature Review") dated September 2015. The Literature Review was updated on December 29, 2016.

Serious legal and scientific concerns regarding use of the epidemiological studies remain unresolved. However, the only EPA documents currently in the public record create a serious misperception of potential risk from use of OPs. The public and now the courts are drawing improper conclusions because the record has not been corrected.

EPA made the right decision in March of 2017 to deny the Pesticide Action Network North America (PANNA)/National Resources Defense Council (NRDC) petition to revoke all tolerances for chlorpyrifos. EPA's press release accurately states:

> By reversing the previous Administration's steps to ban one of the most widely used pesticides in the world, we are returning to using sound science in decision-making -- rather than predetermined results.
>
> * * *
>
> In October 2015, under the previous Administration, EPA proposed to revoke all food residue tolerances for chlorpyrifos, an active ingredient in insecticides. This proposal was issued in response to a petition from the Natural Resources Defense Council and Pesticide Action Network North America. The October 2015 proposal largely relied on certain epidemiological study outcomes, whose application is novel and uncertain, to reach its conclusions.
>
> The public record lays out serious scientific concerns and substantive process gaps in the proposal. Reliable data, overwhelming in both quantity and quality, contradicts the reliance on -- and misapplication of -- studies to establish the end points and conclusions used to rationalize the proposal.

The decision should have also indicated that the epidemiology data are inconsistent and that the Columbia study is severely flawed. New analysis of the epidemiological data has become available

since EPA's March 2017 decision that raises additional concerns about the conclusions drawn in the Literature Review and will be discussed in more detail in this paper.

Policy Shift

The use of the epidemiology data described in the Literature Review is the result of a change in policy and not the result of changes in the underlying science. All recognize that there are sometimes new studies available, such as in the Literature Review, but any new study still must meet the standard of reliability for decision-making. The epidemiology studies described in the Literature Review do not, however, meet the standards put forth in OPP (U.S. EPA, 2016) and other agency guidance. They lack scientific rigor, have severe limitations, and should not be used in EPA's human health risk assessment of OP pesticides.

No formal policy announcement regarding the increased emphasis on epidemiology data has been issued by EPA. However, in 2010, and later updated in 2016, OPP released its *Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides.* This document is not a formal announcement or required approach, but details a draft framework for assessing and using epidemiology data in pesticides assessments (U.S. EPA, 2016). However, OPP states up front that:

> [S]ince the number of pesticides for which quality epidemiology data either exist or are being developed remains relatively low in the near term, experimental laboratory data will likely continue to be the primary source of data for use in quantitative risk assessment for most pesticides.

The desire of political appointees to better incorporate epidemiology data into human health risk assessment is also evident in a Brief Communication published in Environmental Health Perspectives in 2016 (Informing 21st Century Risk Assessments With 21st Century Science, EHP 124:4: April 2016). This communication was authored by Thomas Burke, then Acting Assistant Administrator, U.S. EPA Office of Research and Development; James Jones, then Assistant Administrator, U.S. EPA Office of Chemical Safety and Pollution Prevention; and Linda Birnbaum, Office of the Director, National Institute of Environmental Health Sciences (NIEHS). The communication brief, which was reporting on a 2015 workshop cosponsored by EPA and NIEHS, stated that there is a chasm between risk assessment practices and evolving data from mechanistic and environmental epidemiological studies. The goal, therefore, was to incorporate the environmental epidemiology studies into the risk assessment process.

EPA has been reviewing and incorporating, where appropriate, both epidemiology studies and adverse incident data into the registration renewal process for many years. Industry supports the proper use of robust epidemiology data as an integral part of the overall human health risk assessment process. Prior to Thomas Burke joining EPA, the Agency had not been using existing epidemiology studies described in the Literature Review based on feedback from SAPs, and issues such as lack of access to the underlying data, lack of any clear exposure metrics, and inconsistency with the robust animal toxicity

database. However, that changed with the December 2014 release of the chlorpyrifos Human Health Risk Assessment and the subsequent 2015 Literature Review. The communication brief discusses proposed steps necessary to bridge the current gap between current risk assessment methods and the evolving data from mechanistic and environmental epidemiology studies. Despite the necessary bridging steps described in the communication brief not being resolved, OPP has moved the epidemiology studies to the forefront of OP human health risk assessments.

Thomas Burke's desire to have EPA incorporate epidemiology as the core of human health risk assessments is addressed in Leveraging Epidemiology to Improve Risk Assessment (The Open Epidemiology Journal, 2011, 4, 3-29). This paper laid out Burke's recommendations for enhancing the role of epidemiology data in dose-response and hazard identification. Burke acknowledged that many challenges remain before epidemiology can play a role in the human health risk assessment process --challenges that remain unresolved and raise concern regarding EPA's use of the epidemiology data for the OPs.

Specifically, Burke states that:

> Despite potential advantages afforded by epidemiologic data in assessing dose-response relationships, numerous challenges have repeatedly been highlighted that argue against its use and a reluctance on the part of epidemiologists to participate in the risk assessment process or tailor the reporting of their results for use in risk assessment has been noted. Prominent among these criticisms are issues regarding the sensitivity of epidemiologic methods, limitations of exposure measurements and the potential for confounding and other biases. Further, challenges inherent in interpretation of the results of epidemiologic research may further inhibit its incorporation. Inconclusive results, poor documentation of methods and results, study design flaws, or positive findings in the face of considerable uncertainty may limit the utility of these data in quantification of relationships.

These concerns are consistent with industry's concerns regarding EPA's use of the epidemiology studies in the Literature Review.

It is interesting to note that Burke foresaw that the proper incorporation of epidemiology data into the risk assessment process would reduce uncertainty, rather than increasing it, as is central to EPA's reinstatement of the 10X FQPA safety factor for all OP pesticides.

HED Literature Review

The conclusion of the Literature Review is that epidemiological data creates "uncertainty" for EPA and therefore the 10X FQPA safety factor must be reapplied to all OPs. While several studies are discussed in the Literature Review, EPA stated:

> EPA has conducted systematic reviews of the scientific literature on epidemiology studies on neurodevelopmental outcomes associated with OP exposure in 2012, 2014, and 2015. Although other studies exist, the most robust epidemiology studies are conducted through three major U.S. based prospective birth cohort studies: 1) Mothers and Newborn Study of North Manhattan and South Bronx conducted by Columbia University, referred to in this document as "CCCEH;" 2) Mount Sinai Inner-City Toxicants, Child Growth and Development Study, or the "Mount Sinai Study/Cohort;" and 3) Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by the University of California Berkeley, or "CHAMACOS Study/Cohort."

This document will point out the serious flaws in the epidemiological data cited by EPA -- focusing on the three studies specifically mentioned by EPA above and why using them as the basis for "uncertainty" is an arbitrary policy call made by political appointees in the previous administration and should be changed based on the best available science and data.

Epidemiological Studies

Existing law requires EPA to make a "reasonable certainty of no harm" finding before it can register a pesticide for use. This conclusion was made for OPs based on a robust database of toxicity studies. Existing law also requires that EPA use reliable and available data in its regulatory decision-making. The epidemiological studies do not meet the legal standard of "reliable and available." It is unprecedented and counter to sound scientific judgment to rely on human epidemiologic data as the sole basis for the determination of the need for, and blanket application of, a 10X FQPA safety factor for all OPs based on the issues discussed below.

The Columbia Cohort

The Literature Review gave the most weight to the Columbia study, but this study is fraught with methodological limitations that greatly reduce the reliability of its results.

Exposure Measurement Error

First, the Columbia study relied on a single chlorpyrifos measurement from umbilical cord blood for each child, likely resulting in exposure measurement error. A single measurement cannot capture time-varying levels of chlorpyrifos exposure, and may not correspond to the relevant exposure windows for fetal or postnatal neurodevelopment during gestation or early childhood.

Another source of exposure measurement error may have arisen due to the handling of nondetectable biomarker concentrations. Nondetectable exposures were prevalent; in fact, the investigators did not know exposures for almost half of the study subjects at any point in time. Chlorpyrifos cord blood measurements for 43% of the cohort fell below the limit of detection (LOD), and 12% of the cohort

did not have cord blood measurements available. Rauh *et al.* (2011) used a statistical approach to estimate the unknown values below the LOD, but this approach is known to bias results when the proportion of non-detectable values is greater than 10% (Lubin *et al.*, 2004). Further, for subjects without cord blood data, levels in maternal blood were used as a surrogate, which can lead to exposure measurement error and biased results.

In the Columbia study, as well as the other cohorts, continuous exposure measurements were often grouped into categories. Exposure values were categorized into exposure groups using cut-off values with no biological basis; this may have decreased statistical efficacy and likely biased study findings away from the null.

For example, in the Columbia study, continuous chlorpyrifos levels were not associated with adverse neurodevelopmental effects, but were then categorized into four groups, consisting of concentrations that were less than the LOD (n = 80) and tertiles of those that were detectable (*i.e.*, first tertile, n = 65; second tertile, n = 39; and third tertile, n = 44). Rauh *et al.* (2006) calculated effect estimates for each category *vs.* not exposed (*i.e.*, < LOD) and the only significant association was with lower neurodevelopmental test scores in the group with chlorpyrifos levels in the highest tertile (>6.17 pg/g), but with no exposure-response relationship. Based on these preliminary results, the authors classified subjects into low and high exposure groups defined as below and above 6.17 pg/g (the cutoff between the second and highest tertile), respectively. The description of preliminary results appeared only in the Methods section of the article, as an explanation for the choice of the 6.17 pg/g cut-point to define low *vs.* high exposure. By contrast, in the Results section of the article, Rauh *et al.* (2006) mentioned neither the null findings of their preliminary analysis nor the weaker associations observed for alternative categorization schemes.

Outcome Measurement Error and Confounding

The Columbia study may also have suffered from outcome measurement error and confounding by co-exposures and lifestyle factors. With regard to outcome measurements, several continuous measures of neurodevelopmental outcomes were dichotomized for use in logistic regression, and the choice of cut-points for diagnosing delayed *versus* non-delayed children may have strongly influenced results. In the Columbia study, scores of 85 on the Mental Development Index (MDI) and the Psychomotor Development Index (PDI) were used to distinguish between children who were "normal" *versus* "delayed," but no rationale or citation for this specific cut-point was provided. In contrast, other sources indicate that the typical cut-offs for moderate and severe development delay using the Bayley Scales of Infant Development (BSID)-II are 70 and 55, respectively (Bos, 2013). It is unclear how the choice of cutoffs impacted results; the authors did not conduct sensitivity analyses using more well-accepted clinical cutoffs.

When evaluating neurodevelopmental outcomes, it is critical to account for the many genetic and environmental factors hypothesized to contribute to them. These factors may also be correlated with exposure to chlorpyrifos or other OPs, and thus, may confound the association between OPs and neurodevelopmental effects. Although the Columbia investigators attempted to account for some of these factors, it was not possible to fully account for all of them.

Confounding by socioeconomic status remains a serious concern for the observed neurodevelopmental effects of chlorpyrifos. This is because measures of socioeconomic status are often inaccurate, and thus, residual confounding may persist even when it is included in analyses (Mink *et al.*, 2004). Further, other lifestyle factors, specifically alcohol intake, were not assessed. The prevalence of drinking during pregnancy in the Columbia cohort was estimated to be 25% by study authors, but none of the analyses considered confounding by alcohol use.

Finally, exposure to lead, polycyclic aromatic hydrocarbons (PAHs), and other substances may have also confounded the relationships between OPs and neurodevelopmental outcomes in the available studies. For example, while lead levels were statistically significantly correlated with OP levels of outcomes in the Columbia study, the analysis was based on a subsample of only 89 mother-child pairs, and the test was likely underpowered to detect true associations. Neither OPP nor the researchers considered that small sample sizes and measurement error in covariates limited the statistical power to detect true associations.

TERA Analysis

Toxicology Excellence for Risk Assessment (TERA) is an independent nonprofit organization that focuses on human health risk assessment and education. TERA analyzed the association between chlorpyrifos exposure and neurodevelopmental outcomes reported in one of the most often cited publications from the Columbia study (Rauh *et al.*, 2011) by analyzing the data that were reported in the figures and text of the published article. The TERA analysis, which has been provided to EPA, raises serious concerns about the reliability of the Columbia study data and validity of the Columbia study conclusions. Prior EPA SAPs and other experts have expressed similar concerns. For example: Not all data were included in the Columbia analyses. The study authors admitted to EPA the selectivity of data in their publication, as data from four children with the highest chlorpyrifos levels were removed from the figures; it is possible that the statistical significance of the findings would have changed if they were included. Any missing or excluded data could affect the conclusions and underscore the critical importance of obtaining and analyzing the underlying raw data in order to assess the validity and replicability of the Columbia study claims.

Use of different graphical representations or plots of the data affected trends observed and, therefore, the conclusions drawn. Evidence for effects on IQ scores were eliminated and effects on working memory scores were diminished when data were plotted differently. The impact of simple and more statistically appropriate replotting of the data raises further questions about the scientific validity and strength of conclusions drawn in the Rauh *et al.* (2011) publication. If the reported associations were strong, the conclusions should not have been affected by the method of plotting used.

Despite numerous requests, EPA has not been provided the raw data for the Columbia study and therefore cannot analyze or independently validate the study's conclusions.

Overall, the Columbia study has too many limitations to contribute information regarding chlorpyrifos risks, and it is inappropriate to conclude that it shows that chlorpyrifos causes neurodevelopmental effects. Because this study is unreliable, it does not add any information regarding the likelihood of

an association between OPs and neurodevelopmental effects, and thus, should not be used when considering uncertainty in the overall database.

Other Epidemiology Studies and the Weight of the Evidence for OPs

Overall, there is no consistency among all available epidemiological studies that would constitute a robust and compelling scientific basis for the conclusion that OPs, across the board, are causally associated with adverse neurodevelopmental outcomes in humans (Bouchard *et al.*, 2011; Engel *et al.*, 2011; Donauer *et al.*, 2016; Cartier *et al.*, 2016). Further, there is no evidence of a shared mechanism across OPs that would be responsible for noncholinergic neurodevelopmental effects.

Epidemiology Evidence

Most of the available epidemiology studies, other than the Columbia study, used urinary biomarkers of OP exposure, which are shared for numerous OP pesticides, so a given biomarker concentration may not indicate the same exposures across study subjects or cohorts. Exposure to the preformed metabolite biomarkers from foods at higher levels than the parent OP molecules can also confound the interpretation of the urinary biomarker measurements. Thus, the reliability of any reported association for neurodevelopmental effects across these studies is questionable, as the studies do not link the same exposures to the same effects.

With regard to concurrent consideration of the main OP cohorts, researchers of the Columbia, Mt. Sinai, CHAMACOS, and HOME studies conducted a pooled analysis of the results of these four cohorts in which they assessed associations between prenatal exposure to OPs and child development at 24 months (Engel *et al.*, 2016). The researchers concluded that pooled estimates of prenatal exposure to the OPs and neurodevelopment should be interpreted with caution because of the significant heterogeneity between studies. Such heterogeneity, particularly with respect to differences in enrollment year, target population, gestational age at delivery, and OP pesticide biomarkers, could have biased the pooled estimates of associations. Overall, the pooled analysis by Engel *et al.* (2016) significantly diminishes the case for consistency across the epidemiology studies that was presented in the Literature Review.

Mode of Action

The only common mechanism of toxicity EPA has established for the OPs is cholinesterase inhibition. The most robust and consistent evidence indicates that continuing to regulate OPs based on cholinesterase inhibition (as the rest of the world does) is protective even for neurodevelopmental effects.

EPA readily admits in the HED Literature Review of the organophosphate pesticides that "[a]t this time, a MOA(s)/AOP(s) have not been established for neurodevelopmental outcomes" (page 91, Dec 29, 2016 Literature Review). Even for chlorpyrifos, EPA stated in 2016 that although multiple biologically plausible pathways are being pursued, no one pathway has sufficient data to be considered more credible than others. There continues to be a glaring absence of any plausible biological mode

of action or adverse outcome pathway explanation provided by EPA to describe potential adverse neurobehavioral effects and OP exposure at dose levels below those that produce acetylcholinesterase (AChE) inhibition. There are much more likely biologically plausible causes of the alleged neurodevelopmental effects reported in the epidemiology studies than exposure to chlorpyrifos or other OP pesticides, and these should be fully considered when attempting to establish causality.

Overall, bridging conclusions regarding neurodevelopmental effects to the hazard and risk assessment of all OPs without chemical-specific data and an experimentally demonstrable and accepted common mode of action is scientifically unjustified.

Previous EPA Decisions

The epidemiological data cited in the Literature Review were available to EPA for many years. EPA did not use them in decision-making or as the basis for a 10X FQPA safety factor. On January 25, 2013, Steve Bradbury, the OPP Director at that time, said in an update to the petition filers NRDC and PANNA:

> Thus far, EPA has not encountered epidemiological data of sufficient quality to support quantitative risk assessment of conventional pesticide chemicals. Before EPA decides how to use the epidemiological data on chlorpyrifos, we believe it is critical to attempt to resolve questions about these studies regarding the extent of the cohort members' exposures to chlorpyrifos, as well as the impact of exposure to other compounds capable of causing or contributing to the observed neurological outcomes.

No new data from any of the researchers conducting the epidemiological studies have been provided to EPA since this very clear statement in 2013.

In both the September 15, 2015, and December 29, 2016, releases of the Literature Review, EPA concludes that epidemiology studies do not evaluate consistent outcomes, provide no plausible or tested mode-of-action associated with reported neurodevelopmental outcomes, and fail to report any outcomes below the threshold for cholinesterase inhibition. Quoting EPA (December 29, 2016): "[i]ndeed, there are no studies reporting or even suggesting a lack of AChE inhibition in the dam and/or fetus/pup at any time during dosing. Thus, it is not known whether exposure paradigms that do not inhibit AChE would produce any neurobehavioral effects." This last statement should not be inferred as a statement of uncertainty, but rather a statement of confirmation of the sensitive and conservative use of cholinesterase inhibition as the most appropriate endpoint on which to regulate and be protective of all other toxicities, including neurodevelopmental toxicity. While EPA speculates in the Literature Review that effects in humans may be occurring below the threshold for cholinesterase inhibition, there is no empirical evidence to support this and it is inappropriate and scientifically indefensible to apply a default 10X FQPA safety factor simply because of conjecture. There are robust animal studies (Comparative Cholinesterase Assay and Developmental Neurotoxicity Test) that specifically look for the alleged neurodevelopmental effects observed in the epidemiology studies. Evidence from the

available animal studies clearly confirms that no such effects occur below the threshold for cholinesterase inhibition. In addition, the 10X interspecies uncertainty factor that EPA applies to risk assessments to account for the differences between humans and animals addresses concerns regarding potential neurodevelopmental effects.

Canadian and Australian regulatory authorities also have access to these same epidemiological studies and have concluded they are not sufficient to use in risk assessments for changing endpoints or establishing uncertainty factors and they continue to regulate OPs based on cholinesterase inhibition.

Uncertainty

The purpose of the 10x FQPA safety factor is to address uncertainty from data gaps in the evaluation of risks to children. The many limitations of the epidemiology studies of OPs render their results unreliable and, therefore, unusable for hazard and risk assessment. These limitations do not create uncertainty, particularly the type of uncertainty that the FQPA safety factor is meant to address; rather, they simply make it that the epidemiological studies provide no evidence for or against causation. By contrast, the database for AChE inhibition as the critical effect of OPs is well established and provides evidence for a lack of neurodevelopmental effects without some degree of AChE inhibition. The epidemiology evidence is not strong enough to provide uncertainty regarding neurodevelopmental effects at exposures below the well characterized threshold for inhibition of AChE.

The previous Administration made a policy call that the database for a class of well-researched pesticides was uncertain, owing to a small set of epidemiological studies with substantial limitations. Safety does not and was never intended to mean zero risk nor complete certainty. The Federal Food, Drug, and Cosmetic Act (FFDCA) states:

> *Safe* or *safety* means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance (21 C.F.R. § 170.3).

Further, Congressional intent with respect to uncertainty is described in the committee report for H.R. 13254, which states:

> The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not-and cannot-require proof beyond any possible doubt that no harm will result under any conceivable circumstance.

This was emphasized particularly by the scientific panel, which testified before the subcommittee.

The weak weight of evidence from epidemiological studies does not create uncertainty, and there are robust animal toxicity data that provide EPA with tremendous certainty in meeting the legal standard of a reasonable certainty of no harm.

EPA Can Make a Safety Finding for OPs Using the Existing Animal Toxicity Database

A strong weight of the evidence based on the guideline toxicology and exposure studies continues to permit determinations with reasonable certainty of no harm.

EPA has a robust toxicological database in laboratory animals for all OPs registered in the U.S. and globally, required under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which has historically been used to establish permissible exposures to humans. This database remains robust and constitutes a far greater degree of certainty covering hazard, exposure, and risk of OPs and upon which human safety can be assessed. There is little scientific uncertainty regarding this database. In fact, in EPA human health risk assessments released recently, EPA described the databases as complete and robust.

FQPA was specifically passed to ensure adequate protection of sensitive subpopulations. Thus, EPA required OP registrants to conduct several new studies, such as the Comparative Cholinesterase Assay (CCA), which evaluates potential increased sensitivity in young animals. This study has historically been used by EPA to establish the appropriate FQPA safety factor for individual OPs. Use of the CCA study for FQPA application is more appropriate than the use of existing epidemiological studies for OP compounds, due to their numerous limitations.

Conclusions

EPA has tremendous certainty from the volumes of GLP animal and human toxicity studies (for which it has the data and has independently verified the results) that regulating the OPs based on cholinesterase inhibition is protective of humans including infants and children.

EPA's definition of "uncertainty" (as opposed to the legal definition of uncertainty) is based on weak evidence in a small set of epidemiological studies suggesting associations between *in utero* and child exposure to the OPs and adverse neurodevelopmental behavioral effects in children. These studies do not, however, add uncertainty regarding the safety of OPs. Owing to their numerous limitations, these studies cannot be used to draw any conclusions regarding OPs and neurodevelopmental effects. In contrast, the full weight of the evidence, including animal and *in vitro* studies, support the determination of a reasonable certainty of no harm, and the use of appropriate OP-specific FQPA safety factors based on the animal toxicity database for each OP.

EPA should immediately withdraw the Literature Review from the public dockets, review all the comments submitted regarding the appropriate use of epidemiological data, and specifically address the serious scientific and legal flaws.